

# Renal Hemodynamics and the Renin-Angiotensin System in Cirrhosis

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## ABSTRACT

The interrelationship between renal hemodynamics and the renin-angiotensin-aldosterone system in 28 nonazotemic cirrhotic patients has been studied. Patients were divided into three groups: A) Patients without ascites nor edema; B) Patients with ascites and a relatively high sodium excretion ( $41.9 \pm 12.9$  mmol/day); and C) Patients with ascites and very low sodium excretion ( $4.8 \pm 0.6$  mmol/day). Renin and aldosterone levels significantly increased in group C. A significant correlation was observed between plasma aldosterone concentration and urinary sodium excretion, and between plasma renin activity and aldosterone levels. There were no significant differences in urine flow, glomerular filtration rate, effective renal plasma flow, or renal blood flow between the three groups of patients, in spite of marked differences in renin and aldosterone levels. Renal perfusion was not related to plasma renin activity either in the overall sample of patients or in the individual groups. These results show that factors other than total renal perfusion are involved in renin secretion in cirrhosis.

## KEY WORDS

Cirrhosis, Ascites, Renal hemodynamics, Renin-angiotensin-aldosterone system.

## INTRODUCTION

The mechanisms responsible for renal sodium and water retention in patients with decompensated liver cirrhosis remain still controversial (18).

Several studies have demonstrated that the activation of the renin-angiotensin-aldosterone system is an important cause of renal sodium retention in cirrhosis (2, 5, 7, 8), particularly in non azotemic patients (10, 13). However, the factors involved in the activation of this system in cirrhosis are not completely understood. It was considered in earlier investigations that renin release in these patients could be secondary to a reduction in the renal perfusion (3, 19). In concern with this assumption, it has been reported that renal blood flow is reduced in all groups of cirrhotic patients, even in those with a preserved renal function (14). Nonetheless, other investigators have shown that the renin-angiotensin-aldosterone system may be extremely activated in cirrhotic patients in the setting of a normal renal blood flow and glomerular filtration rate (2, 5).

The present study was, therefore, performed to investigate the interrelationship between renal hemodynamics and the degree of activation of the renin-angiotensin-aldosterone system in non azotemic cirrhotics. The relations between renin, aldosterone and urinary sodium excretion were also studied.

## MATERIALS AND METHODS

The protocol of this study was approved by the local Ethics Committee. We studied 28 cirrhotic patients (19 males and 9 females). Their age ranged from 25 to 70 years. Diagnosis of cirrhosis was made by histology in 25 patients and from clinical and laboratory data in the remainder. The nature of liver disease was alcoholic (14 cases), postnecrotic (5 cases), primary biliary cirrhosis (two cases) and cryptogenic (seven cases). Ascites was demonstrated in 19 subjects in the physical examination or by abdominal ultrasound. No patient was azotemic, and none had hepatic encephalopathy. No patients with cardiovascular or renal disease, fever, neoplasia, diabetes, gastrointestinal bleeding in the previous three weeks, or hematocrit lower than 25 % were included in the study.

Patients were on a sodium restricted diet (40 mmol/day) and on bed rest for four days. Drug therapy, if any, was withheld. On the 5th hospital day, a 24 h urine volume was collected to determine urinary sodium excretion.

On the next hospital day, with the patients being in a supine position, fasting blood samples were drawn at 8 a.m. for the determination of plasma renin activity (PRA), plasma aldosterone concentration (PAC), and hematocrit. Samples for PRA and PAC were collected in ice-cold tubes containing ethylenediaminetetraacetic acid, centrifuged at 4 °C, and the plasma frozen at —30 °C until assayed.

Afterwards, the patients were transferred to a laboratory of Nuclear Medicine for the determination of glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF).

Electrolyte concentrations and the hematocrit were measured by routine laboratory methods. PRA was estimated by radioimmunoassay for angiotensin I (Cea Sorin, France), and PAC by direct radioimmunoassay of plasma samples (Abbot Laboratories, North Chicago, Ill.).

The GFR and ERPF were determined using  $^{99m}\text{Tc}$  DTPA and  $^{131}\text{I}$  labeled hippuran, respectively. A commercially available pack of software was used to carry out these determinations («GFR», User-Generated Software, USA), which is based in the method described by SCHLEGEL and coworkers (6, 16, 17).

Renal blood flow (RBF) was calculated from the ERPF and peripheral hematocrit, according to the following formula:  $\text{RBF (ml/min)} = \text{ERPF (ml/min)} \times (100/[100 - \text{Hematocrit}])$ .

Results are presented as means  $\pm$  SEM. The statistical analysis of the results was made using the Kolmogorov-Smirnov's test to determine the goodness of fit of each sample to a normal distribution, oneway analysis of variance for multiple comparisons and the least squares method for linear regression.

## RESULTS

The patients were divided into three groups: A) cirrhotic patients without ascites nor edema; B) cirrhotic patients with ascites and a relatively high sodium excretion, and C) cirrhotic patients with ascites and very avid sodium retention, the urinary sodium excretion being lower than 10 mmol/day.

The parameters of renal function during the experimental period, PRA and PAC are shown in table I.

Renin and aldosterone levels were significantly increased in patients with lower urinary sodium excretion (group C); and a significant potential correlation was observed between PAC and urinary sodium excretion (fig. 1). A direct correlation was also found between PRA and plasma aldosterone concentration ( $r = 0.871$ ;  $n = 28$ ;  $p < 0.001$ ).

In spite of marked differences in sodium retention and renin and aldosterone levels, there were no significant differences in urine flow, GFR, effective renal plasma flow, nor renal blood flow between the three groups of patients.

There was no significant correlation when ERPF and RBF were plotted versus PRA (fig. 2). However, ERPF and RBF were slightly lower in group C than group B, and in this latter respect to group A. For this reason, partial correlations were performed in each group, and also no relationship could be established between ERPF and RBF with PRA.

## DISCUSSION

The results of the present study are in keeping with previous investigations (5, 10), which have shown that renin and aldosterone levels are increased, in non azotemic

cirrhotic patients with low renal sodium excretion. The major reason for elevated renin and aldosterone concentrations in cirrhosis seems to be an increased secretion of both substances, rather than an impaired hepatic inactivation (2, 15).

Moreover, several studies, and our own results, have constantly found a definite relation between plasma aldosterone concentration and urinary sodium excretion in these patients (2, 5, 10), which suggests a role for aldosterone in sodium retention in normoazotemic cirrhotics.

The case for an important role of aldosterone in sodium retention in decompensated cirrhotic patients is strongly supported by the observation that the longterm administration of spironolactone—a diuretic that exerts its role natriuretic action as an antagonist of aldosterone—may completely reverse sodium retention and ascites in a large percentage of patients with cirrhosis (7, 8).

In addition, hyperaldosteronism seems particularly important for sodium retention in normoazotemic cirrhotics with ascites.

PÉREZ-AYUSO et al. (13) have pointed out that the natriuretic response to spironolactone in these patients is more intense than that obtained when furosemide is administered. If one takes into account the natriuretic potency of each drug, this finding indicates that in cirrhotic patients with ascites and preserved renal function a distal sodium reabsorption, mediated by the action of the aldosterone, is predominating for the impaired sodium excretion.

Some reservations can be made to the hyperaldosteronism as the solely factor for sodium retention. Firstly, in this study, as well as in other investigations (2, 5, 10), a significant number of patients with ascites had a normal aldosterone level. Secondly, when the concentration of aldosterone is diminished in cirrhotic patients by water immersion to the neck, it is not always followed by natriuresis (9).

In our study, as in other investigations (2, 5), a close correlation was established between PRA and plasma aldosterone concentration.

Since PRA in cirrhosis also correlates with the plasma levels of angiotensin II (11), it is reasonable to suggest that the activation of the renin-angiotensin system provides the major stimulus for any increase in the release of aldosterone in these patients.

Supportive evidence to this assumption derive from the fact that renin suppression in these patients, either by head-out water immersion (9) or by the insertion of a peritoneovenous shunt (4), produces parallel changes in plasma aldosterone concentration. In addition, when the action of angiotensin II is interfered by the administration of saralasin (a competitive antagonist of angiotensin II) (1, 20) or captopril (an angiotensin converting enzyme inhibitor) (12, 21), a profound reduction of plasma aldosterone is obtained.

Whether the activation of the renin-angiotensin-aldosterone system is important for sodium retention in non azotemic cirrhotics, a major question is to elucidate what factor or factors are involved in this activation.

Earlier studies showed that PRA was higher in patients with a decreased renal perfusion than in those with a normal renal plasma flow and glomerular filtration rate (3, 19), suggesting that in cirrhosis renin release could be promoted by a reduction of the total renal perfusion. However, in the present study, despite the marked differences in PRA and PAC, there were no differences in the renal perfusion between the three groups of patients, and no correlation could be established between renin levels and the renal perfusion.

This observation agrees with other investigations (2, 5), showing that factors other than total renal perfusion are operative in promoting renin secretion in these patients.

## RESUMEN

Se estudia la relación entre la hemodinámica renal y el sistema renina-angiotensina-aldosterona en 28 pacientes cirróticos no azotémicos. El grupo A incluye pacientes sin ascitis ni edema; el B, pacientes con ascitis y una excreción relativamente alta de sodio ( $41,9 \pm 12,9$  mmol/día); y el C, pacientes con ascitis y una excreción de sodio muy baja ( $4,8 \pm 0,6$  mmol/día). Los niveles de renina y aldosterona están significativamente incrementados en el grupo C. Se observa una correlación significativa entre la concentración plasmática de aldosterona y la excreción de sodio urinario, y entre la actividad de renina plasmática y los niveles de aldosterona. No hay diferencias significativas en la diuresis, en la tasa de filtración glomerular, en el flujo efectivo plasmático renal, ni en el flujo sanguíneo renal entre los tres grupos, a pesar de las marcadas diferencias en los niveles de renina y aldosterona. La perfusión renal no está relacionada con la actividad de renina plasmática ni en la muestra global de pacientes ni en los grupos individuales. Estos resultados sugieren que los factores implicados en la secreción de renina en la cirrosis son diferencias de la perfusión renal total.

## PALABRAS CLAVES

Cirrosis, Ascitis, Hemodinámica renal, Sistema renina-angiotensina-aldosterona.

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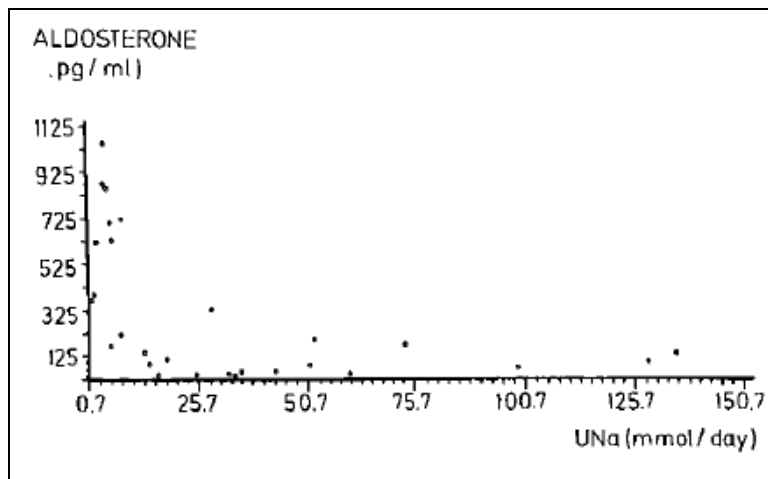
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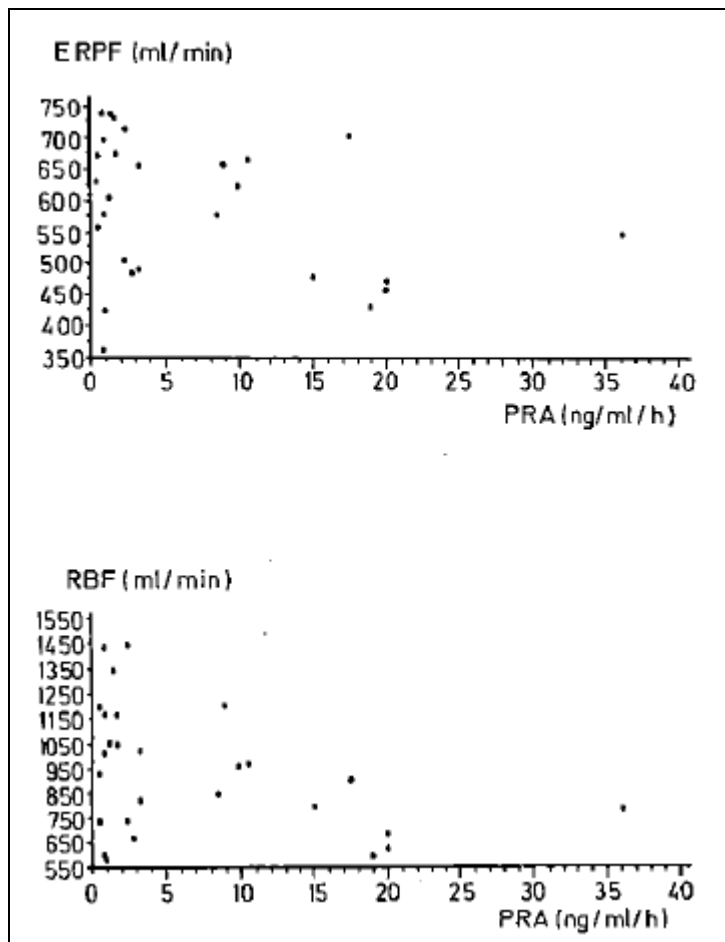
Table 1. Renal function, renin and aldosterone. Results are means SEM

<b>Groups</b>	<b>V (ml/min)</b>	<b>Una (mmol/day)</b>	<b>GRF (ml/min)</b>	<b>ERPF (ml/min)</b>	<b>RBF (ml/min)</b>	<b>PRA (ng/ml/h)</b>	<b>Aldosterone (pg/ml)</b>
A (n=9)	0.57±0.05	59.1±13.1	107.6±7.0	636.2±25.8	1.039.5±85.5	2.86±1.25	112.20±18.34
B (n =8)	0.66±0.09	41.9±12.9	116.9±8.2	586.6±46.5	996.5±99.3	1.78±0.33	105.92±36.12
C (n=11)	0.50±0.04	4.8± 0.6	112.8±8.3	562.5±34.7	840.8±68.0	13.85±3.14	611.09±85.01
P (A-B)	NS	NS	NS	NS	NS	NS	NS
P (A-C)	NS	0.01	NS	NS	NS	0.01	0.01
P (B-C)	NS	0.05	NS	NS	NS	0.01	0.01

V = urine flow. UNa = urinary sodium excretion. GRF = glomerular filtration rate. ERPF = effective renal plasma flow. RBF = renal blood flow. PRA = plasma renin activity. NS = not significant.



**Figure 1.** Relationship between plasma aldosterone concentration and urinary sodium excretion (UNa) in cirrhotic patients ( $r = 0.671$ ;  $n = 28$ ;  $p < 0.001$ ).



**Figure 2.** Relationship between effective renal plasma flow (ERPF) and plasma renin activity (PRA) ( $r = 0.272$ ;  $n = 27$ ;  $p > 0.05$ ); and between renal blood flow (RBF) and PRA ( $r = 0.380$ ;  $n = 27$ ;  $p > 0.05$ ).